



A method development randomised clinical study investigating efficacy of an experimental oral rinse in providing long-term relief from dentinal hypersensitivity

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ABSTRACT

Objectives: To evaluate and compare clinical efficacy of a 1.5% dipotassium oxalate monohydrate (KOX)-containing oral rinse ("Test") for the relief of dentinal hypersensitivity (DH) against Negative Control and Placebo oral rinses, adjunctive to twice-daily brushing with a standard fluoride dentifrice, after 8 weeks.

Methods: This was a randomised, examiner blind, parallel-group, method development study in participants with DH, assessed at baseline and after 4 and 8 weeks by response to an evaporative (air) stimulus (evaluated by Schiff sensitivity score and a 10-point visual rating scale [VRS]) and a tactile stimulus (Yeaple probe). To boost compliance, study features included recruiting only regular oral rinse users, use of an oral rinse during acclimatisation, weekly supervised rinsing and twice-daily text reminders.

Results: After 8 weeks, adjusted mean change from baseline in Schiff sensitivity score was significantly lower in the Test rinse group (n = 43) versus the Negative Control group (n = 23) (difference: -1.22; 95% CI -1.657, -0.782); tactile threshold score was significantly higher in the Test rinse group compared to the Negative Control rinse (difference: 37.46 g; 95% CI: 22.916, 51.995). Similar significant differences in Schiff/tactile scores were also demonstrated after 4 weeks use, after 4 and 8 weeks use as assessed by VRS and as compared to the Placebo rinse (n = 23) in all instances. Study products were generally well tolerated.

Conclusions: The Test rinse showed statistically significant improvements in DH compared to the Negative Control and Placebo rinses after 8 weeks twice daily use. Compliance with the rinsing regimen and study visits was excellent.

Clinical significance: Additional compliance features incorporated into this dentinal hypersensitivity study – recruitment of regular oral rinse users only, acclimatisation rinse, weekly supervised rinsing at the study site, twice-daily text reminders – appear to have been of benefit to the overall study design as compliance was high, and primary and secondary objectives were met.

1. Introduction

The short, sharp pain associated with dentinal hypersensitivity (DH) occurs when exposed dentin tubules are stimulated by tactile, thermal or chemical means, such as with hot food or cold air, causing movement of fluid within these tubules [1–3]. Management of DH can involve home use oral care products that either desensitise the afferent nerve, blocking the pain response, or occlude the end of the dentin tubules, blocking fluid movement following stimulation [4]. Nerve desensitising

agents, such as potassium salts, generally take a number of days or weeks to work, whereas tubule occluding agents (*i.e.*, oxalates, bioglass, strontium and stannous salts, or silicas) generally work more rapidly [5–8].

A number of successful clinical studies have been conducted on oral rinses containing the occluding agent dipotassium oxalate (KOX), available as over-the-counter products [9–11]. Recently, three randomised double-blind, placebo-controlled studies of a similar design were conducted to evaluate the DH efficacy of three different 1.5–2.0% KOX-

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containing (as dipotassium oxalate monohydrate) oral rinses [12]. Statistically significant improvements were found in favor of KOX oral rinses versus a placebo rinse in one of these studies but not the other two. The reason for the lack of statistical differentiation in these studies was unclear as KOX had been shown to be effective in reducing DH in other published clinical studies [9–11].

The mixed results observed by Burnett et al [12] with KOX oral rinses prompted an investigation by conducting this method development clinical study. It has been demonstrated that long-term compliance with dental hygiene instructions is low, at 37% in one follow-up study [13] and 51% in another [14] and it can be hypothesized this may also be the case during clinical studies. Today's society uses mobile phones as their primary mode of communication and there are over four billion mobile phone subscribers worldwide [15]. Text messaging is a fast, cheap and efficient way for people to communicate via their mobile phone. Multiple medical studies report significant compliance benefits when utilising electronic technology to enhance interventions for weight loss, drug adherence, physical activity, smoking cessation and diabetes management, among others [16–19]. One dental study, designed to evaluate oral hygiene improvement in orthodontic patients who received weekly text messages, found greater reductions in plaque, gingival inflammation and bleeding compared to those who did not receive text message reminders [20].

The plan of this study was such that it was used to explore some of the areas of clinical design in a DH study that could be used for examining efficacy of existing and future DH oral rinse technologies. This 8 week method development study aimed to compare clinical efficacy of a 1.5% KOX-containing oral rinse developed for relief of DH compared to a negative control oral rinse and a placebo rinse, all used twice-daily alongside a standard fluoride toothpaste. In this current investigation, efforts were made to ensure compliance in a number of ways including recruiting only regular oral rinse users, using an oral rinse during the acclimatisation period, supervising rinsing at the study site and sending twice-daily phone text reminders to participants.

2. Materials and methods

This was a single center, 8 week, randomised, examiner-blind, three-treatment, parallel-group, method development study with healthy participants with a self-reported history of DH. The study was conducted at a USA-based clinical research center and was approved by an independent review board before initiation (U.S. Investigational Review Board, Inc. Miami, FL, 33143 USA: U.S.IRB2017SRI/05). It was carried out in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice (E6) in agreement with the Declaration of Helsinki. This study was registered at Clinicaltrials.gov: NCT03238352. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

2.1. Participants

The study enrolled healthy participants aged 18–65 years old who were regular oral rinse users with a minimum of 20 natural teeth and a self-reported history of DH lasting more than 6 months but not more than 10 years. General exclusion criteria included pregnancy; breastfeeding; hypersensitivity to study materials; a xerostomia-causing condition or medication; kidney disease, hyperoxaluria or any condition that could be exacerbated by oxalic acid or oxalate salts; use of an oral care product indicated for DH relief within 8 weeks of screening and participation in a clinical study or receipt of an investigational drug within 30 days of screening. General oral exclusions included: requirement for antibiotic prophylaxis for dental procedures; tongue/lip piercings; dental implants; dental prophylaxis within 4 weeks, desensitizing treatment or tooth bleaching within 8 weeks, scaling or root planing within 3 months and gross periodontal disease and/or

treatment of such within 12 months of screening. Specific dentition exclusions for selected test teeth included evidence of current or recent caries or treatment of decay within 12 months of screening; a sensitive tooth not expected to respond to treatment or with contributing etiologies other than erosion, abrasion or facial/cervical gingival recession (EAR); exposed dentin but with deep, defective or facial restorations and teeth with full crowns or veneers, cracked enamel, orthodontic bands or used as abutments for fixed or removable partial dentures.

2.2. Study procedures

At the screening visit, written informed consent to participate in the study was obtained, and demography, ethnicity, medical history, and concomitant medications were recorded. The examiner performed complete oral hard tissue and oral soft tissue (OST) examinations, dentition exclusions, assessment of EAR, gingival status, using the Modified Gingival Index [21], and tooth mobility, using a modification of the Miller scale [22]. A positive pain response was tested via a direct 1 second application of air from a standard dental syringe from a distance of around 1 cm.

Eligible study participants were supplied with a standard fluoride dentifrice (1000 ppm fluoride as sodium monofluorophosphate; Colgate® Cavity Protection; Colgate-Palmolive Company, New York, USA), a toothbrush (Oral-B® Sensi Soft Manual Toothbrush; Procter & Gamble, Cincinnati, OH USA) and a marketed fluoride oral rinse (Crest® Pro-Health Advanced with Extra Deep Clean mouthwash; Procter & Gamble, Cincinnati, OH, USA) to use twice-daily (morning and evening) during the 2–3 week acclimatisation period between screening and baseline visits. These products were selected as they did not contain any known anti-sensitivity ingredients. Additionally, the over-the-counter monograph directions (twice daily) and quantity of use (10 ml) for both rinses were aligned with the directions and quantity of use of the test KOX oral rinse. Each product use was recorded in a provided diary. First use of the acclimatisation dentifrice and oral rinse was carried out under study site supervision.

At the baseline visit (2–3 weeks after screening), eligibility to continue was confirmed with a review of the inclusion/exclusion criteria. Participants underwent an OST examination, followed by tooth sensitivity assessments: a tactile stimulus evaluation using a Yeaple probe [23] with maximum 20 g pressure, then, at least 5 minutes after the tactile assessment, an evaporative (air) stimulus with participant reaction recorded using the Schiff Sensitivity Scale [24] (See 'Assessments' section for details). From the results of these, two non-adjacent test teeth were selected that had a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 .

Eligible participants were stratified according to the maximum baseline Schiff sensitivity score (2 or 3) of the two selected test teeth then assigned to a study group in accordance with a randomisation schedule generated by an independent statistics agency prior to the start of the study, using validated software (SAS version 9.4; SAS Institute Inc., Cary, NC, USA). Randomisation numbers within each stratum were assigned in ascending numerical order according to appearance time for the baseline visit.

Participants were randomised into one of the following groups using a stratified randomised block design with a 2:1:1 ratio:

- Test rinse: Experimental oral rinse containing 1.5% w/w KOX and 0 ppm fluoride;
- Negative Control rinse: Commercially available oral rinse containing 0.02% w/w sodium fluoride (Colgate® Total Daily Repair; Colgate-Palmolive Company);
- Placebo rinse: Oral rinse containing 0% w/w KOX and 0 ppm fluoride.

Participants first carried out their allocated study regimen under supervision at the study site. They were instructed to brush for 1 timed

minute in their usual manner with the standard fluoride toothpaste (Colgate® Cavity Protection) and expectorated. They then rinsed with 10 mL of tap water for 5 seconds and expectorated; then rinsed with 10 mL of their assigned oral rinse for 60 timed seconds and expectorated. No further rinsing with water was permitted after oral rinse use; participants were asked to refrain from eating or drinking for 30 minutes. Participants continued to use their assigned study treatment twice-daily (morning and evening) for the next 8 weeks, recording each brushing and rinsing occasion in the diary provided.

The examiner, study statistician and any other sponsor employees who could influence study outcomes were blinded to the treatment received. Dispensing staff were not involved in any efficacy assessments. While participants' group allocation was not disclosed to them, due to differences in product taste, appearance and packaging (though products were dispensed without commercial labels), participants could not be fully deemed 'blinded.'

All study participants were sent twice-daily (morning and evening) text message reminders requesting them to perform their timed brush and rinse. Participants returned to the study site once each week over the 8 week study period bringing their study kit so that the oral rinse bottle and its contents could be weighed to verify study compliance. Diaries were checked to assess compliance and participants undertook a supervised brushing and rinse.

2.3. Assessments

The assessment of DH using two different stimuli follows the recommendation of Holland et al [6]. Tooth sensitivity was assessed at baseline and then after 4 and 8 weeks of treatment, using first a tactile stimulus (Yeaple probe), then an evaporative (air) stimulus (with Schiff Sensitivity Scale and VRS) on the two selected test teeth only. An OST examination was completed at each of these visits prior to clinical assessments of sensitivity.

Tactile assessments were performed by a single trained examiner using a constant-force (Yeaple) probe. At baseline, a maximum 20 g force was applied; at subsequent visits it was 80 g. Testing began at 10 g and increased by 10 g with each successive challenge until a "yes" response for a painful stimulus was recorded. The force setting which elicited the "yes" response was repeated. If a second "yes" was not obtained, the force setting would be increased by 10 g and continued until a force was found to elicit two consecutive "yes" responses. If no pain response was found, the threshold was recorded as > 80 g.

The evaporative (air) stimulus followed the tactile assessment after at least 5 minutes to allow recovery time. The examiner's assessment of the participant's response to the air stimulus was recorded on the four-point Schiff Sensitivity Scale where: 0 = participant does not respond to air stimulus; 1 = participant responds to air stimulus but does not request discontinuation; 2 = participant responds to air stimulus and requests discontinuation or moves from stimulus; 3 = participant responds to stimulus, considers stimulus to be painful and requests discontinuation of the stimulus [24]. Participants also rated the intensity of their response to the evaporative (air) stimulus using a 10-point visual rating scale (VRS) to mark their pain on a scale of 1 ('no pain') to 10 ('intense pain').

2.4. Safety

A trained dental evaluator performed intraoral examinations at each study visit. All adverse events (AEs) were recorded and monitored throughout the study. The AEs and any observed abnormalities noted during the OST examination were transcribed from the screening visit until 5 days after final use of study product. The investigator determined the causal relationship of each AE using their clinical experience and classed severity as mild, moderate, or severe. Treatment-emergent adverse events (TEAEs) were reported for the safety population, which included all randomised participants who received study

product.

2.5. Data analysis

A sufficient number of people were to be screened in order to randomize at least 100 participants (approximately 50 to the Test rinse, 25 to the Negative Control rinse, 25 to the Placebo rinse groups) to ensure 80 evaluable participants completed the entire study. With this 2:1:1 distribution of participants in the treatment arms the study had less than 50% power to detect a mean treatment difference of 0.36 in the Schiff sensitivity score using a 2-sided *t*-test of significance level 0.05 for the Test rinse against the Negative Control rinse. The standard deviation (SD) used in this calculation was 0.8; this estimate was obtained from a previous study [12]. The Test rinse group was also compared with a combined group comprised of the Negative Control and Placebo rinse groups using the 2-sided *t*-test with the same estimates of mean difference, significance level and SD. In this instance, the study had 51.1% power. All statistical analyses were conducted using SAS 9.4.

Analysis was carried out on a modified intent-to-treat (mITT) population, defined as all randomised participants who received at least one dose of study treatment and had at least one post-baseline efficacy evaluation. The per protocol (PP) population included all participants in the mITT population who had no protocol deviations deemed to affect efficacy.

The primary analysis was a comparison of mean change from baseline in Schiff sensitivity score between the Test rinse and Negative Control rinse regimens at Week 8. Analysis of Covariance (ANCOVA) was used to determine the change from baseline in Schiff sensitivity score at Weeks 4 and 8 with treatment as a factor and mean baseline Schiff sensitivity score as a covariate. Change from baseline in the tactile threshold at Weeks 4 and 8 was analysed using an ANCOVA with treatment and baseline Schiff stratification as factors and baseline tactile threshold as a covariate. Analysis was conducted for the Test rinse versus the Negative Control rinse or the Placebo rinse and also versus a combined group of the Negative Control rinse and Placebo rinse.

The assumption of normality and homogeneity of variance in the ANCOVA model was investigated and, if violated, data transformations were to be investigated. If suitable transformations could not be found, non-parametric Van Elteren tests were to be performed, adjusting for the maximum baseline Schiff sensitivity scores, and results were compared with the ANCOVA results. If the inferences from the two analyses were similar, then both sets of results were to be reported with emphasis on the ANCOVA results. In case of discrepancies between *p*-values of ANCOVA and Van Elteren analysis, inferences were drawn on the non-parametric analysis.

3. Results

A total of 123 participants were screened for entry into the study; 89 participants were randomised (Safety Population) and 85 (95.5%) completed the study (Fig. 1). Overall, most participants were female (88.8%) and were of White/Caucasian/European Heritage (84.3%). The demographic characteristics were similar among participants in each group (Table 1). The first participant entered the study on August 7th, 2017, the last participant finished the study on October 27th, 2017.

For one participant in the Negative Control rinse group and one in the Placebo rinse group, product non-compliance was frequent and outside the 80–120% window. These two participants were excluded from the PP population; however, as it was pre-specified that the PP population was only to be analyzed if more than 10% of the mITT population were excluded, and this was not the case, only the mITT population was analysed.

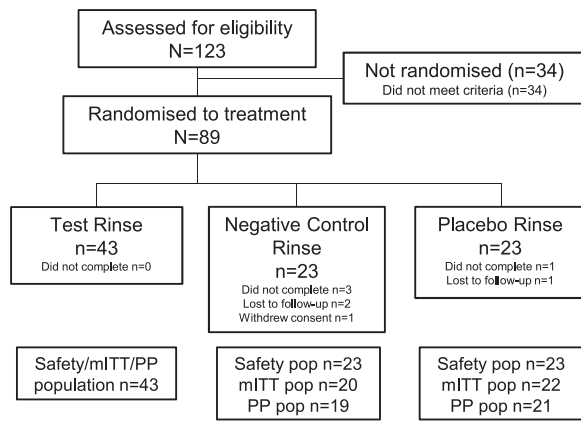


Fig. 1. Study Flow.

mITT: modified intent-to-treat; pop: population.

4. Efficacy

4.1. Schiff sensitivity score

After 8 weeks of treatment, the adjusted mean change from baseline in Schiff sensitivity score showed a greater improvement in the Test rinse group than in the Negative Control rinse group [-1.94; 95% confidence interval (CI): -2.188, -1.697 versus -0.72; 95% CI: -1.085; -0.361, respectively] (Fig. 2). The difference between the adjusted mean scores for the Test rinse and Negative Control rinse groups was -1.22 (95% CI: -1.657, -0.782) and was statistically significant ($p < 0.0001$) in favor of the Test rinse. The Test rinse was also statistically significantly different from both the Negative Control rinse at 4 weeks, and from the Placebo rinse and combined control groups at 4 and 8 weeks ($p < 0.0001$ for all except Test versus Placebo at 4 weeks where $p = 0.0004$) (Table 2).

4.2. Tactile threshold

After 8 weeks of treatment, the adjusted mean change from baseline in tactile threshold was higher for the Test rinse group than the Negative Control rinse group (61.31 g; 95% CI: 53.120, 69.503 versus 23.86 g; 95% CI: 11.848, 35.863, respectively) (Fig. 3). The difference between the adjusted mean scores for the Test rinse and Negative Control rinse groups was 37.46 g (95% CI: 22.916, 51.995) and was statistically significant ($p < 0.0001$) in favor of the Test rinse. The Test rinse was also statistically significantly different from both the Negative Control rinse at 4 weeks, and the Placebo rinse and combined control groups at 4 and 8 weeks ($p < 0.0001$). Assumptions of normality and homogeneity of residuals were investigated; minor departures were observed. Supportive non-parametric results from the Van Elteren test were similarly statistically significant at all time points and for all

comparisons ($p < 0.0001$ for all except Test rinse versus Negative Control rinse at 8 w where $p = 0.0004$) (Table 2).

4.3. Visual rating scale

All VRS scores decreased from baseline (Fig. 4) with most being statistically significantly different at both 4 and 8 weeks in favor of the Test rinse group versus the Negative Control rinse, the Placebo rinse and the combined control groups ($p < 0.005$). The exception was a non-significant difference ($p = 0.069$) between the Test rinse versus the Placebo rinse at 4 w (Table 2).

5. Safety

Overall, six participants (6.7%) experienced six TEAEs (Table 3). All TEAEs were mild/moderate in intensity and had resolved by study completion. Two participants (2.2%) reported two TEAEs that were considered treatment-related: one report of mild oral discomfort in the Test rinse group; one report of mild oral mucosal exfoliation in the Placebo rinse group. There were no deaths, no serious AEs, no medical device incidents, and no participants with AEs that led to discontinuation of treatment or withdrawal from the study.

6. Discussion

In this study, significant improvements in DH were demonstrated when using an experimental 1.5% w/w KOX-containing oral rinse for 8 weeks compared to using Negative Control and Placebo rinses when each was used as an adjunct to twice-daily brushing with a standard fluoride toothpaste. It is believed that participant perception scales such as VRS can sometimes be less reliable for measuring DH than examiner derived scores such as Schiff Sensitivity Scale, as responders tend to concentrate scores in one area of the scale [25]. However, in this study the trends observed for VRS were aligned with those for the Schiff Sensitivity Scale and tactile threshold scores, with the greatest reduction in DH being consistently observed for the Test rinse group.

KOX was selected as the Test oral rinse as this oxalate-based occluding agent has been shown to be effective in reducing DH [9–11]. In a previous series of three studies, the experimental 1.5% w/w KOX-containing oral rinse showed statistically significant DH efficacy compared to a placebo oral rinse in one study, but no significant differences were found in the other two [12]. To optimise the study design and help to ensure compliance, the current method development study included a number of new features that were not considered in the earlier oral rinse studies. For instance, only regular (twice-daily) oral rinse users were recruited such that the rinsing habit had already been established and the rinse instructions would be similar to their normal oral hygiene practice. This study also included an oral rinse during the acclimatisation period, whereas in Burnett et al [12] only a toothpaste was used at this stage. This was introduced to minimise potential placebo/

Table 1

Demographic characteristics (safety population).

		Test rinse (N = 43)	Negative Control (N = 23)	Placebo (N = 23)
Sex, n (%)	Male	6 (14.0)	4 (17.4)	0
	Female	37 (86.0)	19 (82.6)	23 (100)
Race, n (%)	African American/African heritage	6 (14.0)	2 (8.7)	3 (13.0)
	White/Caucasian/European/Arabic heritage	37 (86.0)	20 (86.9)	20 (87.0)
	American/Alaskan native	0	1 (4.3)	0
Age	Mean (SD)	46.0 (9.27)	41.5 (9.76)	43.0 (8.75)
	Range	24–61	24–58	28–58
Stratification ^a	Schiff score 2	9 (20.9)	5 (21.7)	5 (21.7)
	Schiff score 3	34 (79.1)	18 (78.3)	18 (78.3)

ⁿ(%) = number (percent) of participants; SD = standard deviation.

^a Maximum baseline Schiff score.

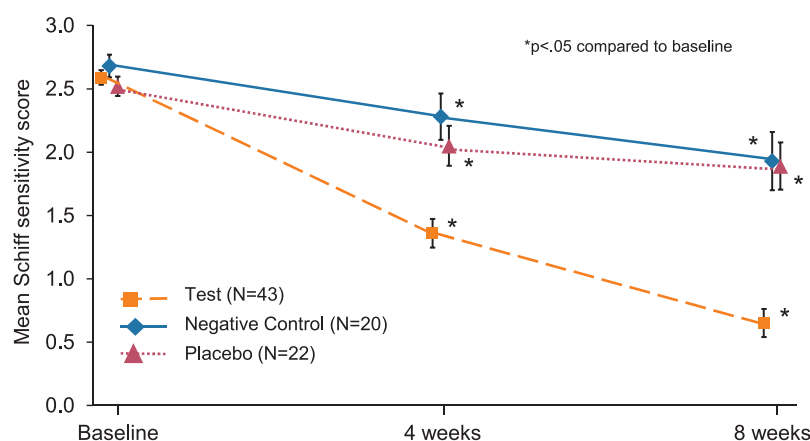


Fig. 2. Schiff sensitivity scores by time and treatment (modified intent-to-treat population).

Data are offset for clarity.

(Publication note only: To be in colour for online, greyscale for print).

Hawthorne effects and to standardise participants' oral care regimen, given that there would be no change in regimen moving from the acclimatisation period to the test period.

As a number of studies have found that the use of text message reminders can enhance study compliance [16–20], here, twice-daily text message reminders were sent to participants. They also undertook a weekly supervised brushing and rinsing at the study site, during which they were asked to measure out the 10 ml dose of oral rinse to confirm and correct any deviations from the regimen instructions. Participants were also asked to bring their assigned oral rinse bottles at each visit so that the contents could be weighed and compliance assessments could be confirmed. As a result of these changes, compliance was extremely high and only two participants were deemed non-compliant with the brushing/rinsing regimen.

One limitation of this study is that there were several exclusions in terms of the selected study population. As this was a method development study, the population needed to be controlled in such a way that enabled the effect of the added compliance features to be observed. Further studies may require less stringent exclusions to be able to extrapolate data to the general population.

In conclusion, additional compliance features incorporated into this DH study – including recruiting only regular oral rinse users, addition of using an oral rinse during the acclimatisation period, weekly

supervised rinsing at the study site and twice-daily text reminders – appear to have been of benefit to the overall study design as compliance was high and all primary and secondary objectives were met. The findings of this study add weight to other studies showing the utility of a 1.5% w/w KOX-containing oral rinse in lowering symptoms of DH.

Declaration of Competing Interest

This study was funded by GSK Consumer Healthcare, of whom SY, AB, M Araga and M Atassi are employees. KM and JM are Directors of Salus Research, Inc, which has received funding from GSK Consumer Healthcare.

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Table 2

Statistical analysis of change from baseline in evaporative (air) Schiff sensitivity, tactile threshold and VRS scores (mITT Population).

Treatment comparison		Difference (standard error) ^a [95% CI] p-value		
		Schiff sensitivity score	Tactile threshold score	VRS score
Week 4	Test rinse vs Negative Control	−0.87 (0.201) [−1.273, −0.473] < 0.0001	29.96 (7.035) [15.963, 43.962] < 0.0001 ^c	−1.35 (0.456) [−2.256, −0.440] 0.0041
	Test rinse vs Placebo	−0.72 (0.194) [−1.107, −0.334] 0.0004	28.66 (6.816) [15.094, 42.224] < 0.0001 ^c	−0.82 (0.445) [−1.705, 0.067] 0.0695
	Test rinse vs Combined Control	−0.80 (0.161) [−1.116, −0.477] < 0.0001	29.31 (5.645) [18.077, 40.544] < 0.0001 ^c	−1.08 (0.368) [−1.815, −0.352] 0.0042
Week 8	Test rinse vs Negative Control	−1.22 (0.220) ^b [−1.657, −0.782] < 0.0001	37.46 (7.306) [22.916, 51.995] < 0.0001 ^d	−2.06 (0.527) [−3.108, −1.010] 0.0002
	Test rinse vs Placebo	−1.28 (0.213) [−1.705, −0.858] < 0.0001	49.88 (7.079) [35.791, 63.966] < 0.0001 ^c	−1.72 (0.514) [−2.742, −0.695] 0.0013
	Test rinse vs Combined Control	−1.25 (0.176) [−1.600, −0.901] < 0.0001	43.67 (5.862) [32.001, 55.334] < 0.0001 ^c	−1.89 (0.425) [−2.734, −1.044] < 0.0001

^a Difference is first named treatment minus second named treatment such that a negative (Schiff sensitivity score, VRS score) or positive (tactile threshold score) difference favours first named treatment.

^b Primary comparison.

^c Supportive non-parametric analysis $p < 0.0001$.

^d Supportive non-parametric analysis $p = 0.0004$.

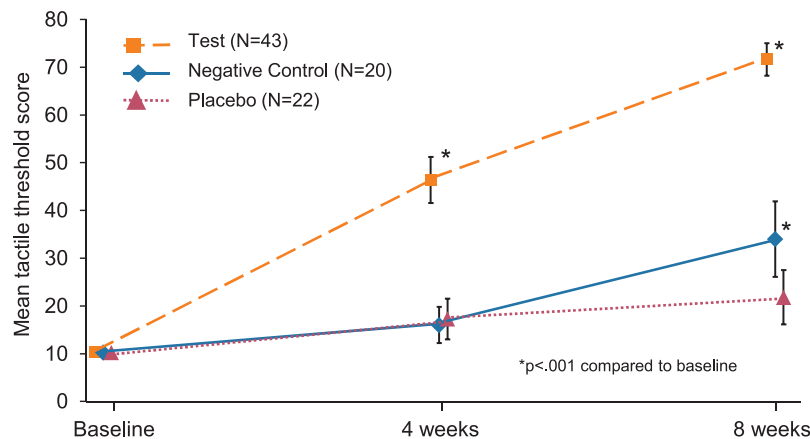


Fig. 3. Tactile threshold scores by time and treatment (modified intent-to-treat population). Data are offset for clarity. (Publication note only: To be in colour for online, greyscale for print).

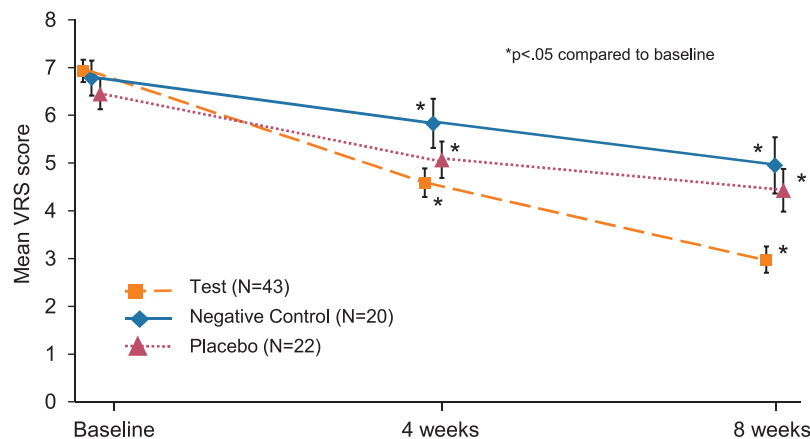


Fig. 4. VRS scores by time and treatment (modified intent-to-treat population). Data are offset for clarity. (Publication note only: To be in colour online, greyscale in print).

Table 3
Treatment-emergent and treatment related adverse events (safety population).

	Test rinse N = 43		Negative Control N = 23		Placebo N = 23	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
At least one TEAE	4 (9.3)	4	0	0	2 (8.7)	2
Oral TEAE	4 (9.3)	4	0	0	1 (4.3)	1
Treatment related						
Oral discomfort	1 (2.3)	1	0	0	0	0
Oral mucosal exfoliation	0	0	0	0	1 (4.3)	1

n(%) = number (percent) of participants; nAE = number of adverse events.

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